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Report to the
Scientific Grants Committee of the British Medical Association.

REPORT ON THE
COCA ALKALOIDS.

BY

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REPORT ON THE COCA ALKALOIDS.

OUR PRESENT KNOWLEDGE OF THE ALKALOIDS FOUND IN COCA.

SINCE the leaves of the coca plant have been worked on a large scale for the extraction of cocaine, it has become apparent that there is obtained from them, besides cocaine, a considerable quantity of amorphous substance having the easily recognised chemical reactions of alkaloids. The end result of treating the leaves is usually a mixture of cocaine with more or less amorphous material, but as cocaine and its salts crystallise readily from many menstrua, while the other substances do not, a separation can thus be effected, and by repeated crystallisation from alcohol pure cocaine salts may be easily enough obtained.

The accompanying amorphous material got by different manufacturers varies greatly in quantity, composition, and appearance, owing probably to differences in the process employed and in the amount and nature of the alkaloids originally present in the leaves. There has been great divergence of opinion regarding its exact composition, but it now seems probable that the specimens examined by the various observers were by no means identical. Some of them consisted almost entirely of crystallisable cocaine mixed with hygrine and other bodies, being thereby prevented from crystallising;[1] while others were a mixture of alkaloids,[2] prevented from crystallising by the presence of impurities. The amorphous substance consists largely of a single alkaloid, which has been named isatropylcocaine by Liebermann,[3] and has been very fully described by him. Hesse described two new bases under the names cocaidine[4] and cocamine,[5] but he is now of opinion that cocaidine is a mixture, and that cocamine is identical with isatropylcocaine.[6] Lately, Einhorn[7] has signalised the discovery of another alkaloid, but very little is as yet known about it.

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[1] Stockman, *Pharm. Journ. and Trans.*. xvii, (3), 861, 1887.

[2] Lyons, *Amer. Journ. of Pharmacy*, October 17th, 1885.

[3] Liebermann, *Ber. d. deutsch. chem. Gesellsch.*, xxi, 2342, 1888.

[4] Hesse, *Pharm. Jour. and Trans.*, xviii, (3), 437, 1887.

[5] Hesse, *Ibid*, 71.

[6] Hesse, *Berichte*, xxii, 665, 1889,

[7] Einhorn, *Berichte*, xxii, 339, 1889.

With our present knowledge, the total quantity of alkaloids, other than cocaine, in the leaves can only be roughly estimated, but it is, relatively speaking, very considerable, and must have a marked effect in determining the action of coca. In attempting an estimation we have, however, some data to go by. Owing to the deterioration in quality which the leaves suffer in transit, there is now made in South America a large quantity of "crude cocaine," this being a mixture of all the alkaloids which can be extracted. It is a perfectly white amorphous powder, often in masses, has a tobacco-like odour, and yields crystalline cocaine when treated with proper solvents. Dr. Squibb informs me that the mixed product from the Truxillo leaf is considered to yield about 50 per cent. crystallisable cocaine, while that from the Huanaco leaf yields about 75 per cent. In a sample examined by Dr. Paul[8] 42 per cent. only was present. The amorphous alkaloids are thus seen to vary from 25 to 58 per cent. of the total alkaloids obtainable from coca. In any case they must be an important constituent, for if we take the amount of cocaine in the leaves as, roughly speaking, 0.5 per cent., then their proportion will be about from 0.2 to 0.6 per cent. Hesse states that in one variety of leaf there is 0.6 per cent. cocamine (isatropylcocaine) and that the amorphous alkaloids vary in amount and nature according to the leaves from which they are derived.[9] As we shall see later on, cocamine has a very definite physiological action, and its presence is doubtless of great importance to the coca chewer.

The substances, some of the actions of which I propose to describe in this paper, are ecgonine, benzoylecgonine, cocaine, and cocamine, while I have added a short note on hygrine. All of them do not exist ready formed in the leaves. Ecgonine probably never does so, and benzoylecgonine only when (owing to bad drying and heating) it has become formed from the decomposition of cocaine. Cocaine and cocamine can readily be extracted from the leaves, while hygrine seems to be a decomposition product. A closer study and more prolonged experience of coca cultivation will be necessary before our knowledge on many chemical and economic points can be regarded as anything like complete. As yet hardly a beginning has been made.

Ecgonine is the basis of all the above alkaloids (except hygrine, probably), and chemically they are to be regarded as ethers of ecgonine. As there is now a considerable degree of certainty about the chemical constitution of these bodies, it may be of interest to go into this in detail, more especially as the subject is one well fitted to illustrate the present state of our knowledge regarding the chemistry of some of the more successfully investigated alkaloids. Before doing so, however, I wish to express my sense of indebtedness to Dr. Hesse (Feuerbach), Dr. E. R. Squibb (Brooklyn), Professor Crum Brown, and Messrs. Hopkins and Williams, for the assistance which they have afforded me in carrying on this investigation.

CHEMISTRY OF ECGONINE AND ITS DERIVATES.

I. *Ecgonine.*—Ecgonine is an alkaloid having the formula $C_9H_{15}NO_3$, and crystallises with one molecule of water in colourless glassy prisms. Its taste is feebly bitter sweet; it is very soluble in water, less so in absolute alcohol, and insoluble in ether. The reaction is neutral, it forms crystalline salts with acids, and is not precipitated from a watery solution by caustic alkalies. It is obtained from cocaine by heating the latter with strong acids or bases, when it decomposes into ecgonine, methylic alcohol, and benzoic acid.[10]

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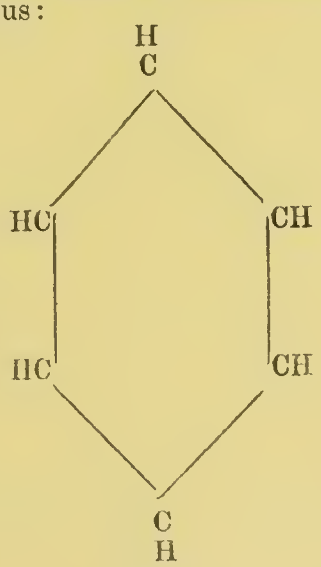
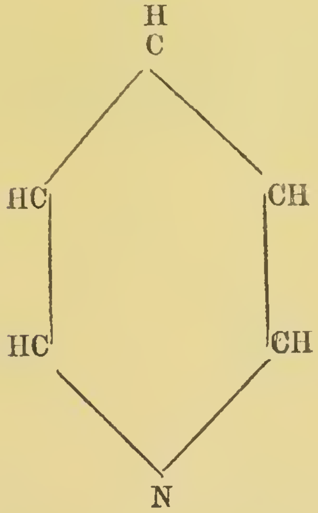
[8] Paul, *Pharm. Journ. and Trans.*, March 17th, 1888.
[9] Liebermann, Einhorn, Hesse, *Berichte, loc. cit.*

Ecgonine, like so many other alkaloids, is constituted on the same type as pyridine, of which it is a derivative. Pyridine itself is regarded by chemists as benzol in which one CH has been replaced by N. Using the simplest constitutional formulæ, they may be represented thus:



Benzol C_6H_6



Pyridine C_5H_5N

As alkaloids are substituted ammonias, we must consider the hypothetical body C_5H_5 in pyridine as a triatomic radical, taking the place of the three hydrogen atoms in ammonia ($N-C_5H_5$). The nitrogen and carbon atoms in pyridine are all ready to form *addition* compounds by simply adding on new bodies, while the hydrogen atoms can be easily replaced, and thus *substitution* compounds formed. The added and substituting bodies themselves may contain replaceable hydrogen, and this further increases the possibility of enlarging the molecule. By simply glancing at the pyridine ring one can see how numerous and complex are the bodies which may be thus formed from it. It has been shown[11] that ecgonine, which is known to be the basis of all the coca alkaloids (except hygrine), is methyl-tetrahydropyridyl—β-oxy-propionic acid, and has the following chemical constitution. Tetrahydropyridine is pyridine *plus* four atoms of hydrogen ($C_5H_5N.H_4$), each attached at different points of the ring; while methyl-tetrahydropyridine is the same body with one of its hydrogen atoms replaced by methyl (CH_3), and may be written:

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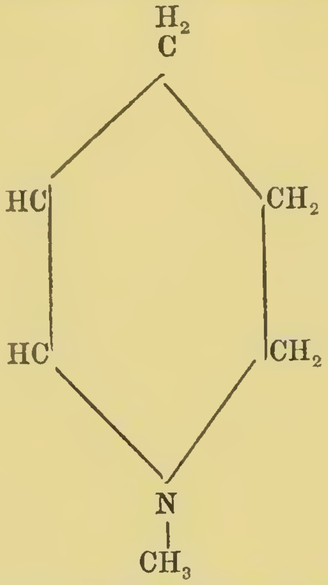
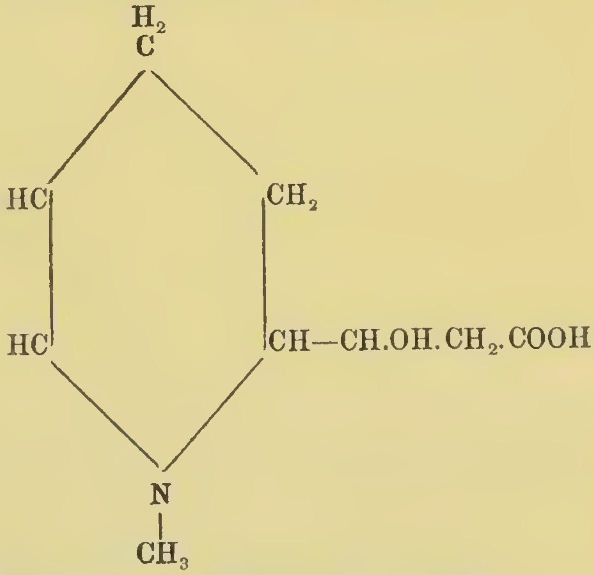
[10] Lossen, *Liebig's Annalen*, cxxxiii, 351, 1865.

[11] Calmels and Gossin, *Comptes Rend.* 100, 1143, 1885; C. E. Merck, *Ber. d. deutsch. chem. Gesellsch*, xix, 302, 1885; Einhorn, *ibid.*, xxi, 1221, 1887.



$C_5H_5N(CH_3)H_3$.

Into the molecule of methyl-tetrahydropyridine there has been introduced β-oxypropionic acid $C_3H_6O_3$ (CH_2. OH. CH_2. COOH), each body losing one atom of hydrogen in the process. This gives us ecgonine ($C_9H_{15}NO_3$), which may be represented thus:



or CH_3 — $N=C_5H_7$ — $CHOH=CH_2—COOH$.
methyl tetrahydropyridyl β-oxypropionic acid

II. *Benzoylecgonine.*—Benzoylecgonine ($C_{16}H_{19}NO_4$)[12] can be formed readily from cocaine or its salts by simply heating them with water. It crystallises with four molecules of water, is fairly soluble, and is not precipitated from its watery solution by alkalies. On heating with strong hydrochloric acid it yields ecgonine and benzoic acid. Structurally it is ecgonine in which one H atom has been replaced by the acid radical benzoyd (OC. C_6H_5). The substituted hydrogen atom is not in the pyridine nucleus, but in the β-oxypropionic acid. The formula is therefore

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[12] Skraup, *Monatshefte f. Chemie*, 556, 1885; W. Merck, *Ber. d. deutsch. chem. Gesellsch*, xviii, 1954, 1885; Paul, *Phar. Journ. and Trans.*, Oct., 1885; Einhorn, *Berichte*, xxi, 47. 1888.

$$\underset{\text{methyl}}{CH_3} \; - \; \underset{\text{tetrahydropyridyl}}{N{=}C_5H_7} \; - \; \underset{\text{benzoyl-}\beta\text{-oxypropionic acid}}{CH.\ O\ (OC.\ C_6H_5).\ CH_2\ COOH.}$$

III. *Cocaine.*—Cocaine ($C_{17}H_{21}NO_4$) and its salts are in well-formed crystals, the salts being very soluble in water, the base slightly so. It is precipitated from watery solution by caustic-fixed alkalies, and by ammonia, the precipitate being soluble in excess, but re-forming after a few minutes in the case of ammonia. It is a very unstable body, and readily decomposes when simply heated with water as follows:

$$C_{17}H_{21}NO_4 + H_2O = \underset{\text{benzoylecgonine}}{C_{16}H_{19}NO_4} + \underset{\text{methyl alcohol}}{CH_4O}$$

When heated with acids or alkalies the decomposition is more complete

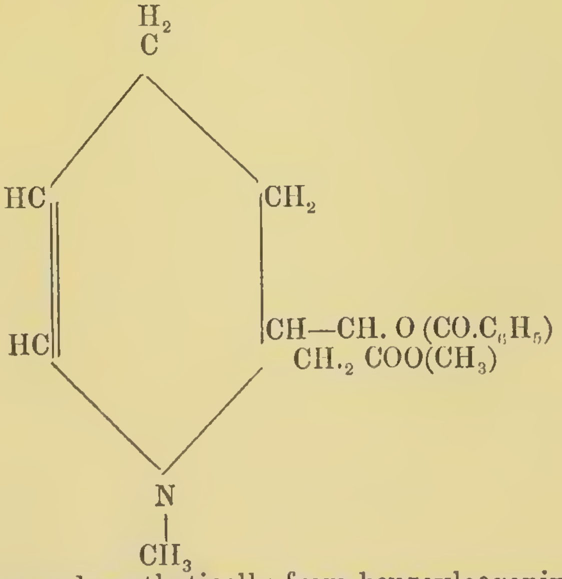
$$C_{17}H_{21}NO_4 + 2H_2O = \underset{\text{ecgonine}}{C_9H_{15}NO_3} + \underset{\text{benzoic acid}}{C_7H_6O_2} + \underset{\text{methyl alcohol}}{CH_4O}$$

Cocaine is thus methyl-benzoyl-ecgonine, or ecgonine in which two H atoms have been replaced respectively by the alkyl-radical methyl and the acid-radical benzoyl. Both of them are introduced into the β-oxypropionic acid. The formula is therefore

$$\underset{\text{methyl}}{CH_3} \; - \; \underset{\text{tetrahydropyridyl}}{N = C_5H_7} \; - \; \underset{\text{methyl-benzoyl-}\beta\text{-oxypropionic acid}}{CHO\ \overbrace{CO.C_6H_5}^{\text{benzoyl}}\ .\ CH_2\ .\ COO\overbrace{CH_3}^{\text{methyl}}}$$

Einhorn[13] assigns the following structure as the most probable:

$C_{17}H_{21}NO_4=$



Cocaine has been prepared synthetically from benzoylecgonine[14] and from ecgonine,[15] while a number of its homologues have also been made and described. Ethylbenzoylecgonine ($C_{16}H_{18}$ (C_2H_5)

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[13] Einhorn, *Berichte*, xxi, 3029, 1888.

[14] Skraup, *loc. cit.;* Einhorn, *Berichte*, xxi, 47, 1888; W. Merck, *Berichte*, xviii, 2264, 1888.

[15] W. Merck, *Berichte*, xviii, 2952, 1885; Liebermann and Giesel, *Berichte*, xxi, 3196, 1888; Einhorn and Klein, *Berichte*, xxi, 3335.

NO_4) has been prepared by Merck[16] and by Novy[17], while the latter has also formed monobromethylbenzoylecgonine ($C_{16}H_{18}$ (C_2H_4Br) NO_4), propylbenzoylecgonine ($C_{16}H_{18}$ (C_3H_7) NO_4), and isobutylbenzoylecgonine ($C_{16}H_{18}$ (C_4H_9) NO_4). We have also methylcinnamylecgonine,[18] methylisovalerylecgonine,[19] methylphenylacetylecgonine,[19] and methylanisylecgonine.[20] The actions of these bodies have not been fully investigated, but they are said to resemble cocaine closely, and to be powerful local anæsthetics.

IV. *Cocamine* (*Isatropylcocaine Truxillin*).—Isatropylcocaine ($C_{19}H_{23}NO_4$) is identical with Hesse's cocamine, and has been most fully described by Liebermann.[21] It is obtained from the amorphous substance got as a by-product in the manufacture of cocaine from the truxillo leaf. On heating in a sealed tube with hydrochloric acid it splits up thus:

$$C_{19}H_{23}NO_4+2H_2O=\underset{\text{ecgonine}}{C_9H_{15}NO_3}+\underset{\text{isatropic acid}}{C_9H_8O_2}+\underset{\text{methyl alcohol.}}{CH_4O}$$

Liebermann obtained two isatropic acids, which he calls γ and δ respectively. They are isomeric with α- and β-isatropic acids, and also with tropic and cinnamic acids, but differ from them in chemical properties.[22] Isatropylcocaine is therefore a body constituted in the same way as cocaine, but in which the radical of isatropic acid is present instead of the radical of benzoic acid; it is methylisatropylecgonine (methyltruxillylecgonine).

The specimens which were used in my experiments I obtained from Dr. Hesse and from Dr. Squibb's residues (No. 3)[23], by purification. The amorphous mass was dissolved in acid water, washed with ether, treated with animal charcoal, and then precipitated with caustic potash. Only the middle fraction was used, so as to obtain a homogeneous body, and this was further purified by frequent solution and precipitation. To make sure that it could contain no cocaine, it was digested for twenty-four hours with solution of caustic potash, and then filtered. The caustic potash would dissolve up any cocaine readily, while cocaine is only somewhat soluble in it. It was then washed with water, dissolved in very weak hydrochloric acid, and precipitated with ammonia. After being collected on a filter, washed and dried, it forms a pure white non-crystalline powder. Its solution in acids rapidly becomes yellow in colour, and it does not disappear readily when heated with water, as cocaine does. After several days heating in the waterbath, it slowly disappears, forming a slightly brown solution, from which it can be again precipitated by alkalies. Cocaine has been prepared artificially from ecgonine, γ-isatropic acid, and methylic alcohol.[24]

PHYSIOLOGICAL ACTION OF THE ALKALOIDS.

I. *Ecgonine.*—The ecgonine was obtained from Merck, or prepared by myself from cocaine, benzoylecgonine, and the amorphous residues. It is necessary to use the base itself ($C_9H_{15}NO_3 . H_2O$), as the hydrochlorate remains extremely acid, even after washing with ether and heating to 120° C. for some hours.

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[16] W. Merck, *Berichte*, xviii, 2952.

[17] Novy, *Phar. J. and Trans.*, xviii, [3] 233, 1887.

[18] Liebermann, *Berichte*, xxi, 3372.

[19] Einhorn and Klein, *loc. cit.*

[20] Liebermann, *Berichte*, xxii, 130, 1889.

[21] There is some uncertainty regarding the name by which this base is to be known. Recently Liebermann (*Berichte*, xxii, 782, 1889) has altered its name to truxillin, while the acids derived from it he calls α-, β-, and γ-truxillic acids. Under the circumstances, it seems most advisable to retain the name cocamine originally given to it by Hesse.

[22] See Liebermann, *Berichte* xxii, 124, 1889.

[23] For Squibb's method of obtaining cocaine and the amorphous residues see *Ephemeris* iii, 1101, 1888.

[24] Liebermann, *Berichte* xxii, 130, 1889

Frogs.—Ecgonine is not a powerfully acting substance, so much so, that unless large amounts are given, the fact that it has any action at all may be entirely overlooked. In cats and rabbits very large doses have no apparent effects, so that I have been able to investigate its action on frogs only. In the latter animal the central nervous and muscular systems are the parts chiefly affected. As regards dosage, 0.05 gramme must be considered a small dose for a frog, while 0.5 gramme was the largest which I administered, and it did not prove fatal. In one case, however, 0.2 gramme and in another 0.3 gramme was lethal. When 0.05 gramme is given to a frog, subcutaneously or by the mouth, the only symptom is a slight increase in the reflexes, occurring generally about an hour after administration and lasting for a few days. With larger doses there are seen at first dulness, lethargy, and inco-ordination of movement, but only to a trifling extent, as the animal can easily be roused up, and jumps quite well when irritated. These symptoms are undoubtedly due to slight depression of the brain and spinal cord; their duration is variable, but they seldom last longer than a few hours, and often before they have worn off a well-marked increase in the spinal reflex excitability is observed. This increase is often greatest on the second or third day, and lasts usually for many days, being a very much more prominent symptom than the depression, which can easily be overlooked after a moderate dose.

At the place of injection (if the ecgonine be given subcutaneously) the muscles gradually become considerably diminished in electric irritability, but in very few cases, and then only after the lapse of some days, are they quite irresponsive to stimulation. If the poison be given *per os*, the spinal symptoms come on rapidly, while the muscles throughout the body are more equally affected, those which receive the largest blood-supply being most deeply poisoned. In different frogs, even of the same species, there seems to be a considerable diversity in the rate and amount of the absorption of ecgonine by the muscles, which probably accounts for the supervention of increased reflex excitability being later in some cases than in others. The muscles pass into a condition of rigor mortis, and in doing so sometimes contract so much as to alter the normal attitude of the animal. For example, if the ecgonine have been injected under the skin of the back, the contraction of the dorsal extensor muscles may gradually bend round the spinal column until the back forms a deep concavity, the attitude of the frog being so changed that it can no longer jump.

The reason for the long persistence and comparative mildness of the spinal reflex increase probably is that the muscles absorb the poison, and only slowly give it out again to enter the circulation and act on the cord; for, if the spinal cord be exposed and a few drops of a watery solution of ecgonine be applied to it, the increased reflex comes on in about half an hour, and may amount to tetanus. When administered in any other way than by direct application to the cord tetanus is never observed, this seeming to prove that ordinarily the poison reaches the cord only in small quantity. In such cases the tetanus is accompanied by a great tendency to exhaustion (see experiment VI). These questions will be discussed at more length later on, as they are common to all the substances under investigation.

In the fatal cases the heart was found stopped in diastole and very dilated. Death occurred only after many days, apparently from stoppage of the heart and extension of the rigor to a large number of muscles.

Ecgonine appears to have no marked, if any, local anæsthetic action, as a 20 per cent. solution applied to the eye of a cat and to my own tongue did not diminish sensibility.

When the alkaloid is given subcutaneously or by the mouth, the motor nerves are not appreciably affected. If, however, ecgonine dissolved in water (0.15 in 0.6 cubic centimètres), be injected directly into one iliac artery, the sciatic nerve of the same side gradually becomes depressed, and in about eighteen hours is quite inexcitable to electric stimulation. The muscles of the same leg also lose their excitability, but not so rapidly.

Mammalia.—In a rabbit 2 grammes and in a kitten (1¼ kilogrammes) 2 and 5 grammes had no effect (subcutaneously) beyond very slight transient excitement and dilatation of the pupils.

In conclusion, there can be no doubt that ecgonine has a slightly different action on the two species of frog—rana temporaria and rana esculenta—when given in the same dose to frogs of the same size; the difference is more apparent than real, however, and depends entirely on the amount given. A dose which, in the former, depresses the spinal cord and visibly poisons the muscles, causes in the latter only an increase in the reflexes, but with a considerably larger dose we get here also the symptoms of depression. In rana temporaria also smaller doses cause death. To illustrate this and other points, I give at length a number of the experiments.

Experiment I.—Rana temporaria, 28 grammes. 12.8. 0.1 ecgonine (Merck's) in ½ cubic centimètre water under skin of back. 12.20. There has been no change. 12.50. Is slightly sluggish, but jumps quite well. 1.10. Sluggish, will lie on back if very gently turned over; slight but well marked increase in reflexes; jumps are vigorous, but movements not exactly co-ordinated. 1.35. Lies with head down on table, but if stimulated jumps quite well, although not very precisely; reflexes increased. 4.10. Has remained pretty much in same condition.

Second day. Reflexes more exaggerated; if frog be stroked, it draws itself together spasmodically.

Third to eighth day. The increase in reflexes is still present; frog very unwilling to jump, as it gets a shock on landing.

Ninth to fifteenth day. The increased reflex gradually wore off, until on the fifteenth day it was barely perceptible; the frog was then killed, and all its muscles found to be quite excitable.

Experiment II.—Rana temporaria, 32 grammes. 12.0. 0.2 ecgonine (Merck's) in ⅔ cubic centimètre water under skin of back. 12.15. Rather duller; jumps well but heavily. 1.15. About same. 3.45. The reflexes are now increased.

Second day. Reflexes slightly increased; in the evening they were greatly increased, and the frog was active and lively.

Fourth day. Reflexes increased; active and jumps well; back is slightly arched concavely.

Fifth to eighth day. Reflexes remained increased, while the back gradually got more and more arched.

Ninth to tenth day. Reflexes increased; back so much curved that head is pulled upwards and backwards, and the frog rests on its belly; its position is so altered that it cannot jump.

Eleventh day. Died; muscles of back do not contract to strong electric current; the other muscles contract well at 80 millimètres (Du Bois induction apparatus); motor nerves quite excitable; heart in diastole, and does not contract to electric stimulation.

Experiment iii.—Rana esculenta, 47 grammes. 11.35. 0.2 ecgonine (Merck's) in ⅔ cubic centimètre water under skin of back. 11.42. Slight increase in reflexes; jumps well and actively. 11.46. Reflex increase is now very distinct, but not great. 3.0. Has been same; very active and lively, and slight increase in reflexes.

Second to ninth day. There was a very slight increase in reflexes, which gradually passed off.

Experiment iv.—Rana esculenta, 42 grammes. 2.22. 0.5 ecgonine (from pure cocaine) in 1 cubic centimètre water under skin of back; jumped about actively for a few minutes. 2.26. Distinctly less active. 2.30. Duller, and lets its legs lie out behind, but if stimulated jumps quite well; reflexes slightly diminished. 3.0. Dull and disinclined to move, but will not lie on back; jumps well if disturbed. 5.30. Dull, but reflexes are now exaggerated.

Second to third day. Dull and very unwilling to move, but there is marked increase in reflexes; when irritated jumps, but rather heavily and clumsily, and the effort is followed by exhaustion.

Fourth day. Dulness passed off. There is great increase in reflexes, almost to tetanus; pupils small.

Fifth to ninth day. Increase in reflexes gradually diminished.

Twelfth day. Increase now scarcely noticeable.

Eighteenth day. Still alive and well.

Experiment v.—Rana temporaria, 35 grammes. 1.30. 0.3 ecgonine (from cocamine) *per os*. 1.35. Slight increase in reflexes. 1.45. Reflexes considerably increased; pupils dilated; jumps well. 2.30. Gives marked start on slight stimulation. 5.10. Increased reflex now almost amounts to tetanus.

Second day. Reflexes greatly exaggerated; pupils large.

Third to fourth day. Reflexes remain increased, but the muscles are deeply affected, and frog is getting much weaker.

Fifth day. Reflexes still exaggerated, but very feeble in its movements.

Sixth day. Died; muscles of abdomen and anterior part of back are non-excitable to electricity, those of posterior part of back, thighs, and legs contract very faintly to a strong current; sciatic nerves give, on stimulation, no muscular contraction; heart in diastole.

Experiment vi.—Rana temporaria; spinal cord exposed. 12.36. Few drops sol. ecgonine (Merck) on cord. 1.0. Slight increase in reflexes; there has been very slight diminution. 2.0. Greatly increased reflex. 3.0. Reflexes much greater; gives a violent spasmodic stretch when stimulated. 3.45. Has now tetanus. 5.30. Much exhausted; lying flaccid; when stimulated gives only a spasmodic twitch.

Second day. Sitting up; reflexes increased; much recovered.

Third day. Reflexes still very greatly increased; killed.

Benzoylecgonine.—For a full description of the action of benzoylecgonine I must refer the reader to a former paper,[25] where it is given at length; here I can only embody a short summary of the results obtained. When 0.003 to 0.004 gramme is administered subcutaneously to a frog, the only symptoms observed are slight muscular stiffness, and on the third or fourth day a slight increase in the reflex excitability. With 0.006 to 0.02 gramme there ensue, in about half-an-hour, muscular stiffness and great disinclination to move about, while the gait is walking, or toadlike. This is followed in 18 to 24 hours by a great increase in the reflexes, amounting to tetanus in many cases, and lasting for several days. The muscles in the immediate neighbourhood of the place of injection gradually pass into a condition of rigor mortis, which is usually complete at the end of the first day, while those at a distance are unaffected, or only very slightly impaired in excitability: 0.03 gramme is a fatal dose, and may cause death without any spinal symptoms from rapid paralysis of the heart and voluntary muscles. The action of benzoylecgonine is very similar, therefore, to that of caffeine, the muscular and central nervous systems being primarily and chiefly affected, while the heart is involved much less markedly, and the peripheral nerves not at all. Direct application of benzoylecgonine solution to the spinal cord causes tetanus in a very short time, and hence the conclusion may be drawn that the late supervention of spinal symptoms after subcutaneous injection is due to the poison being at once absorbed by the muscles in the immediate neighbourhood, and only slowly excreted by them to circulate in the blood, and act on other organs. The voluntary muscles must have a great power of absorbing benzoylecgonine, as shown by the fact that those with which it first comes into contact rapidly imbibe it, those which are more distant receiving at first none, or very little. It is only after some days that the latter become markedly diminished in electric excitability. Non-striped muscle is affected to a much less degree. When a large number of muscles have been poisoned, or when the spinal symptoms have been severe and long-continued, death ensues.

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[25] Stockman, *Journ. Anat. and Physiol.*, xxi, 46, 1886.

Rabbits were extremely insusceptible, doses up to 2 grammes, given subcutaneously, producing no effect except slight diarrhœa. In cats, however, 1 gramme caused excitement, great dilatation of pupils, very great increase in the reflexes, and diarrhœa: 1.7 gramme caused violent tetanus, extreme diarrhœa, and death from exhaustion in six hours. The *post-mortem* appearances were extremely striking. The muscles did not respond to stimulation, the small intestine presented a moniliform appearance, and was so contracted as to occlude the lumen, while the bladder was also extremely contracted. The heart's action was comparatively little affected until just before death, which seemed to be due to failure of respiration.

III. *Cocaine: Action on Frogs: Summary and Criticism of Previous Investigations.*—The results of my experiments with cocaine on frogs have led me to conclusions differing in some respects from those of previous observers, and hence it is necessary to give a very short *résumé* of what has been already done. In the various descriptions we find so many discrepancies, that a suspicion is at once aroused that the investigations have been carried out with widely different substances. As we shall see, there is serious disagreement regarding both the exact symptoms and the dose required to produce them. The statements as to the lethal dose are also much at variance. The earliest experiments with cocaine were made by Schroff,[26] who used a preparation obtained from Merck; but, from the description given of its physical characters, it does not seem to have been quite pure. Doses of 0.005 to 0.02 gramme were given. The former caused lessening of activity of voluntary movement and respiration; medium doses caused deeper torpor, while after large doses the animal lay as if dead; the heart was much depressed, and death ensued. Stimulation of the central nervous system, muscles, or motor nerves gave no reaction. Schroff regarded cocaine as a narcotic, but he has failed to describe some of the most prominent symptoms in frogs. It may now be concluded with certainty that the substance which he used in his experiments was a mixture of the coca alkaloids, as the lethal dose given (0.02 gramme) is much too small for pure cocaine. The passage in which he describes the action of medium doses on frogs is, perhaps, worth quoting at length:—"One bridge after another which connects the organism with the outer world is broken. The nictitating membrane falls over the eye, the brain shuts itself out from sound, the skin no longer conveys external impressions; all movements, even slight respiration, stop, and only the heart works on quietly and strongly caring for the inner organism. Thus the frog lies, sunk in the deepest ego of a brute soul, left to the calm contemplation of itself." He regards its action as similar to that of Indian hemp, and diametrically opposed to that of caffeine.

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[26] Schroff, *Wochenbl. d. Gesellsch. Wiener Aerzte.* 1862; Schmidt's *Jahrbücher*, cxvi, 297, 1862.

F. Jolyet[27] obtained a more correct idea of the cocaine action on frogs, and summarises his results in four paragraphs. He found that (1) very small doses of a soluble salt excite sensibility and decrease motility; (2) larger doses cause loss of power over co-ordination of movement, loss of power of movement from one place to another, while sensibility is entirely retained; (3) still larger doses induce diminution and ultimate disappearance of sensibility, the excito-motor power being never lost; and (4) in fractional doses characteristic tetanus is caused.

The most complete account is given by von Anrep.[28] He found that what he calls very small doses (1 to 2 milligrammes hydrochlorate of cocaine subcutaneously) had no effect, or sometimes caused a stage of excitement marked by restlessness and increased reflex, lasting altogether about ten minutes. Medium doses were 0.005 to 0.01 gramme, and were followed by active movements succeeded soon by quietude. On slight stimulation of the skin there were marked contractions amounting almost to tetanus, and abortive attempts to jump. The frog soon lay quite helpless, and only on violent stimulation gave a slight reflex twitch. This also soon disappeared, and it then lay as if dead, but recovered in a few hours. Larger doses had the same but more marked effects, and anything above 0.04 gramme was fatal.

The spinal reflexes were first slightly increased, and then depressed with small doses, while 8 milligrammes and upwards caused depression from the beginning. The motor nerves were depressed but never completely paralysed, while the sensory nerve-endings and trunks were quite paralysed by large doses. Very small doses are reported to have increased the sensitiveness of sensory nerves, and left the motor untouched.

Striped muscle was unaffected, and gave normal tracings; with medium and large doses the pupils were dilated. The next three references I have had to take from von Anrep's paper, as the originals were not obtainable. Nikolsky (1872) found that $\frac{1}{10}$ milligramme caused restlessness and excitement, larger doses caused the same symptoms and then paresis, while 2 milligrammes were fatal to a frog from stoppage of the heart. The striped muscles were unaffected, but the spinal cord and all the nerves were paralysed.

Danini, after 0.005 to 0.015 gramme, observed sometimes short-lived excitement, and then rapid weakening of voluntary movements. There was a transient decrease of reflexes, then an increase. Motor nerves remained quite excitable, the most persistent symptom being muscular paralysis. Tetanus was never observed.

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[27] F. Jolyet, *Comptes Rend. de la Soc. de Biol.* (4) iv, 162, 1867.

[28] Von Anrep, *Pflüger's Archiv*, xxi, 38, 1880.

Moreno y Maiz,[29] with 0.015 gramme of cocaine acetate, got a slight stage of excitement, then paralysis of hind legs, cessation of motion and respiration, and recovery in twenty-four hours. Gramme 0.007 caused in fifteen minutes great excitement with violent movements, but inability to jump. Sensibility remained intact. After 0.045 gramme there was speedy general paralysis, but the motor nerves remained excitable. When this dose was given in portions, Moreno got a characteristic tetanus.

Buchheim and Eisenmenger [30] give details of four experiments on frogs—0.0025 gramme subcutaneously in one case and 0.005 gramme in three. Respiration soon ceases, then rapidly occurs great weakness, sensibility is long maintained, and on each stimulation there is a twitch, although a faint one. The thigh muscles are excitable at death, but soon lose their excitability. They find the action similar to that of caffeine, but not so pronounced. It is interesting to note that one hour and a half after administration of 0.0025 gramme, they obtained from the isolated gastrocnemius muscle curves exactly resembling those got after caffeine and theobromine, namely, an extremely long period of contraction. Only one frog survived after 0.005 gramme.

Ott[31] must have experimented with a substance containing little or no cocaine. Thus he finds 0.005 gramme a lethal dose, and describes well-marked tetanic convulsions and muscular stiffness as results of much smaller doses. He found also that it increases and prolongs muscular contraction.

A. Bennett[32] finds the action of cocaine identical with that of caffeine. He ascribes to caffeine, however, the power of producing local anæsthesia, an observation which no subsequent observer has been able to confirm. In several other respects his results as to caffeine and cocaine have not been confirmed.

Mays[33] compares cocaine to brucine in its action. After administration of 5 milligrammes hydrochlorate he got in a frog paresis, one convulsion, and then gradually paralysis, but when he gave 0.0106 gramme there were convulsions in three minutes, which lasted for nearly three hours, and persisted after severance of the cord from the brain. Complete paralysis ultimately supervened. As he compares its action to that of brucine, the tetanic spasms must have been a very prominent feature.

U. Mosso[34] found hydrochlorate of cocaine more energetic in its action than von Anrep did. Thus he considers 0.005 to 0.01 gramme a large dose. The symptoms in frogs are described as those of narcotic poisoning—respiration ceases, the eyes sink, the head droops, the muscles become flaccid and lose their tonicity. The conducting and reflex power of the cord is rapidly lost, and it is affected long before the sensory and motor nerves are, the irritability of the motor nerves being depressed only after large doses, and in a late state of the poisoning. He shows also that von Anrep was mistaken regarding the early and deep paralysis of the sensory nerves and their terminations. Convulsions were never seen.

Berthold[35] has shown that cocaine is a muscle poison, as its direct application in solution to the sartorius muscle and heart of the frog, or its injection into the anterior chamber of the eye in rabbits and cats, caused muscular paralysis without previous stimulation. In the case of the sartorius the paralysis was peculiar, as tetanising stimuli induced not a tetanus, but a single strong contraction, the amount of which, on repeated stimulation, fell to *nil.* After a rest of half a minute to a minute the muscle recovered its original power of contraction, but rapidly lost it again on stimulation. In the experiments on the frog's muscle the muscle must have been indirectly stimulated through the nerve, as we shall see later on that it is the latter, and not the former, which suffers from this exhaustion.

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[29] Moreno y Maiz, Recherches chim. et physiol. sur l'Erythroxylum Coca du Pérou et la Cocaine. Paris. *Thèse.* 1868.

[30] Buchheim and Eisenmenger, Eckhard's *Beiträge zur Anat. und Phys.* v, 120, 1870.

[31] Ott, *Toxicological Studies.* Philadelphia. 1874.

[32] A. Bennett, *Edin. Med. Journ.*, xix, part i, 323, 1873.

[33] Mays, *Therapeutic Gazette*, June, 1885, 372.

[34] U. Mosso, *Archiv f. expt. Path.*, xxiii, 153, 1887; *Archives Italiennes de Biol.* viii, 323, 1887.

[35] Berthold, *Centralbl. f. med. Wissensch.*, 1885, 146.

Sighicelli[36] has, on dogs, confirmed Berthold's observation that the pupillary muscles are paralysed, and has shown, in addition, that the muscles of the eyeball and of the intestine are rendered non-excitable to electricity after direct application of cocaine hydrochlorate in solution.

Alms[37] found that the injection of 0.25 cubic centimètres of a 5 per cent. solution into the iliac artery of a frog caused complete paralysis of the sciatic nerve in two minutes, while the muscles were only somewhat diminished in excitability. Painting the skin with a 5 per cent. solution also affected the underlying muscles slightly. Further, he showed that the local anæsthesia is due to an action on the sensory nerve-endings, and not to local anæmia.

Kobert[38] states that cocaine in small doses does not affect the muscle-curve in the frog, nor the power to raise a weight. Large doses cause the curve to be irregular in size. He gave up to 9 milligrammes without causing any immediate symptoms, while in one case convulsions are reported to have occurred on the second day. It is evident, therefore, that he was working, not with cocaine, but most probably with benzoylecgonine.

The later observers—Alms, Berthold, Mosso, Sighicelli—experimented, no doubt, with pure cocaine salts, while Jolyet, von Anrep, and Moreno probably had a nearly pure substance. The others must have worked with mixtures of the coca alkaloids, probably containing in many cases little or no cocaine. What body Mays had it is impossible exactly to say, but Buchheim and Eisenmenger, Nikolsky, and some of the others most probably worked with cocamine. The actions described have a generic resemblance to the action of cocaine, but they seem to differ from it chiefly by producing in some cases marked convulsions, and in others pronounced muscular paralysis, while the lethal dose is much smaller.

Tumass[39] has shown that the application of a solution to the exposed cortex cerebri diminishes its electric irritability. We may therefore take it as proved that cocaine paralyses all forms of nerve-tissue when brought into contact with them, and, further, that it has a slightly paralysing effect on muscle.

My own Experiments. — The general symptoms produced in frogs have not been closely analysed by any previous observer, and this is what I now propose to do. My experiments were made with very fine samples of Howard's and Merck's hydrochlorate of cocaine, and with the base prepared from these by careful precipitation with liquor ammoniæ. The frogs used were rana temporaria and rana esculenta. I must agree with U. Mosso that the doses called small by von Anrep (1 to 2 milligrammes) have much more effect than the latter attributes to them. Mosso thinks that this is probably due to von Anrep having used larger frogs than he did, but I also used large specimens of rana esculenta, and am inclined to think that von Anrep's hydrochlorate of cocaine was by no means pure. It was procured from Merck long before there was any commercial demand for the drug, and at a time when its extraction was not well understood. When the demand for it arose our first supplies of cocaine were amorphous and extremely impure.

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[36] Sighicelli, *Archives Ital. de Biol.*, viii, 128, 1886.

[37] Alms, *Archiv f. Anat. u. Phys.* (Suppl., Heft), 1886, 293.

[38] Kobert, *Archiv f. expt. Pathologie*, xv, 22, 1882.

[39] Tumass, *Archiv f. expt. Path.*, xxii, 107, 1887.

Very Small Doses.—In small frogs (22 to 24 grammes) the hypodermic injection of half a milligramme of the hydrochlorate of cocaine dissolved in water causes slight torpor and heaviness of movement, as if the animal were faintly narcotised. The normal activity of the brain and spinal cord, manifested by the frog's usual appearance of alertness, is evidently depressed, as is also sharp reaction to very slight stimuli. There is often slight paresis of the hind limbs, which are not so closely drawn up to the body as usual; and there may be slight inco-ordination of movement, but the motor power is quite well preserved, the animal moving and jumping vigorously when irritated. The slight dragging of the posterior extremities is (as we shall see later on) a symptom of the sensory rather than of the motor depression. The pupil is increased in size, and there is no stage of excitement. Recovery takes place in one to two hours. In large frogs, one-half to one milligramme causes similar symptoms.

Experiment VII.—Rana temporaria. 24 grammes. Respirations 64 in 30 seconds. 12.28. ½ milligramme cocaine hydrochlorate in ⅓ cubic centimètre water under skin of back. 12.35. Is scarcely so active; respirations 63. 12.45. Sits with head on table; jumps heavily; respirations 60. 12.55. Paresis of hind limbs; jumps heavily when stimulated; struggles if placed on back, but cannot recover; respirations 42 in 30 seconds; pupils dilated. There has been no sign of increased reflex. 1.8. Rather less sluggish, recovers with difficulty when placed on back. 1.20. Is now more active; pupils dilated still. 1.40. Nearly recovered; pupils still large. 2.30. Is quite recovered.

Small Doses.—When 2 or 3 milligrammes are given, the symptoms are more characteristic. The frog shortly becomes torpid, sluggish and awkward in its movements, respiration is slowed, and the pupils are dilated. The nervous system is evidently depressed. It soon lies flaccid on its belly, with its head resting on the table and its legs limply extended. Sensitiveness to external stimuli is much diminished, the animal makes no response if its skin be gently stroked or if its legs be gently shifted, but with slight pinching of the toe or skin it struggles violently and kicks out its legs in a manner which shows that its motor powers are perfectly retained. This characteristic condition, in which the frog lies quite flat on its belly unable to jump or to co-ordinate its movements, but struggling and kicking out vigorously when irritated, has been noticed more or less fully by many previous observers. The reflex reply to sensory impressions is exaggerated, the extension of the legs being tetanic in its intensity, but at the same time there is a certain degree of flaccidity about it. The animal lies quite limply, and although each stimulation calls forth a reflex, yet the spasm is only momentary and the frog never becomes rigid. The condition resembles that seen after large doses of morphine, or in the late stages of strychnine poisoning when there is exhaustion of the cord. Soon, sensory impressions are more difficult to produce and their reflex motor results become feebler, until there may be simply a faint twitch on stimulation.

Before this last stage is reached, however, the frog passes through a rather peculiar condition as regards its reflexes. On pinching the toe a violent spasmodic reflex is obtained, but on repeating the stimulation this gets weaker, and on the third or fourth time there is no response. After a short rest another spasmodic but flaccid movement can be elicited. The centres in the cord are evidently in a condition of easy exhaustion, and it seems as if they had lost their power of properly conserving and distributing their energy, and were compelled, when a sufficient stimulus is applied, to discharge it all in one great effort. With such small doses as 2 or 3 milligrammes a very short time is required for them to recover after each discharge. Electric stimuli applied high up are readily enough conveyed along the cord, and cause contraction of the leg muscles every time. The motor and sensory tracts are no doubt somewhat depressed, because cocaine paralyses every kind of nerve-tissue, but the amount of depression is small with the above doses, and is only sufficient to prevent the conduction of weak stimuli. The non-appreciation of slight stimuli, such as stroking the skin, is accounted for by the depression of the sensory tracts in the cord, while the sensory centres are also dulled to a considerable extent. Owing to this, so-called spontaneous convulsions are never observed.

The condition of the cord can hardly be called one of increased reflex excitability, because it is less sensitive to weak stimuli, but there is (along with depression of conductivity) a peculiar state of the grey matter, in which, when impressed by a sufficient stimulus, it cannot control the amount of energy to be discharged, but exhausts itself in one violent spasmodic effort.

During the progress of the poisoning the frog loses its power of localising a sensory impression. This can be shown by placing a small piece of paper moistened with acetic acid on the skin, when the animal at first removes it in the ordinary way. But very shortly afterwards such an application only causes an irregular struggle, without any attempt being made at removal; and still later no notice whatever is taken of it. At this time, pinching the skin or toe gently with forceps will cause violent struggles. From this we learn, first, that the sense of locality is lost sooner than the sense of pain, just as one would expect. The loss arises not from peripheral but from central causes, as the localisation of a sensation demands a more perfect condition of the central nervous system than its mere perception. Cocaine has, however, disturbed the nerve-centres in the cord and brain just so much that, while the frog feels the pain or the stimulus, it is unable to localise their exact position, this condition deepening until even pain is not felt. We also learn that sensory impressions conveyed from the terminations of peripheral nerves in the skin (acetic acid paper) are not felt at a stage of the poisoning when stimulation of the nerve-stems themselves (pinching skin in forceps) is readily perceived. This point we shall return to later on.

In passing, I should like to point out that this interference (when much short of complete abolition) with the sensory—and consequently the co-ordinating—powers of the spinal cord reproduces symptoms closely resembling some of those seen in locomotor ataxia in man. In both cases they arise from similar causes, namely, defective conduction of sensory impressions by the cord.

The second stage of cocaine poisoning in the frog then gradually comes on. The torpid condition passes off; the animal sits up; the reflexes are increased as in slight strychnine poisoning, and this increase lasts for some days longer, when the frog returns to its normal condition. With such small doses the muscles and motor nerves are not appreciably affected.

Before discussing the action of cocaine further, I quote two illustrative experiments.

Experiment VIII.—Rana temporaria. 46 grammes. Respirations 23 in 10 seconds. 12.41. 0.002 cocaine hydrochlorate (Merck's) subcutaneously in water. 12.43. Movements heavier; is sluggish. 12.45. Respirations 15; pupils large; moving restlessly, but very awkward and cannot jump; no response on stroking skin. 12.48. Torpid and very heavy; lying on belly; respirations 7. 12.52. Ceased to respire; pupils dilated; lets legs lie out behind, and does not respond to stroking skin, but if the toe be ever so slightly pinched the legs are kicked out in a spasmodic fashion. 1.20. Has been *in statu quo*. 1.52. Head now slightly raised from table; cannot jump; does not feel stroking skin, but kicks out violently if pinched; respires occasionally; pupils large. 2.15. Sitting up; jumps heavily; reflexes increased on slight stimulation; pupils very dilated. 2.45. Great increase in reflexes; jumps fairly well; pupils much dilated. 3.45. Very active and lively. 4.30. Jumps well, active and lively; reflexes increased; pupils much dilated.

Second day. Reflexes active; frog lively; pupils large but not fully dilated.

Third day. Reflexes slightly exaggerated; is nearly normal.

Experiment IX.—Rana esculenta. 55 grammes. 12.18. 0.003 cocaine hydrochlorate (Merck's) subcutaneously in water. 12.23. Heavy and awkward; co-ordination of movements bad; pupils very large; no reflex on stroking skin, but pinching toe causes a spasmodic kick out. 12.28. Lying on belly; cannot jump; pupils much dilated; otherwise same. 1.20. Very torpid; pupils very dilated; when pinched there is a spasmodic reflex, but on the third or fourth time the cord ceases to respond and the animal remains flaccid. 4.30. Has been *in statu quo*.

Second day. Frog active and lively; reflexes much increased; when the frog jumps the shock of landing causes a violent tetanic start; pupils dilated.

Third day. Marked reflex; active and lively.

Fourth day. Same.

Tenth day. The reflexes have continued slightly exaggerated.

We can now analyse more carefully the action of cocaine given in the above doses. The central nervous system is much more deeply affected than the peripheral, owing, no doubt, to its much richer blood-supply. The brain activity of the frog is greatly depressed, while the sensory and motor conducting tracts, and the grey matter of the cord, are all much affected. The symptoms produced by the implication of these several parts of the cord are not, however, equally prominent, especially at first. In showing this we may utilise some experiments made by Vulpian[40] and by Alms. Vulpian found that if he divided the spinal cord in a frog high up, and painted the skin of one leg with a 2 per cent. solution of cocaine hydrochlorate, the skin became anæsthetised, and the leg, instead of being drawn up in the ordinary flexed position, lay out "*à l'abandon*," and was trailed helplessly after the body when the frog jumped or moved, exactly as if it were in a condition of motor paralysis. If the animal were irritated in any way, however, this leg was drawn up at once, and hence the motor paralysis is only apparent. Nor does the anæsthetised leg make any attempt to remove a piece of acetic acid paper placed on any unæsthetised part of the body, while the other leg does so at once. Vulpian explained the apparent motor paralysis by assuming that the normal attitude of the frog is maintained by means of slight stimuli passing from the skin to the co-ordinating centre; these are no longer conveyed from the cocainised skin, and hence the leg lies "*à l'abandon.*"

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[40] Vulpian, *Comptes Rend.* xcix, 885, 1884.

Alms confirmed this explanation by more careful experiments, and showed that after the skin of one leg is painted, stimulation of either sciatic is equally effective, and hence there is no real motor paralysis. He also performed the following experiment. A glass plate was inserted under the lumbar plexus on one side, and the nerves painted with a 5 per cent. solution. There ensued loss of sensation in the skin of the same side, and the leg was dragged as if paralysed. The motor paralysis was, however, only apparent, for if the forearm were pinched the leg was moved reflexly and vigorously.

Are we to conclude from this that when a mixed nerve is painted with a 5 per cent. solution of cocaine hydrochlorate, the sensory conduction is interfered with while the motor is not? Alms says no, and for the following reasons. A rabbit's skin may be severely irritated without causing signs of great pain, but if a nerve-stem be gently stimulated in any way, the animal at once exhibits symptoms of suffering. The explanation of this is that the sensory terminations of nerves in the skin cannot sum up and transmit to the stem for conduction to the sensory centres a given stimulus in its maximum intensity, while a direct stimulation of the stem is so carried to these centres. When a mixed nerve-stem is painted with cocaine solution, the motor and sensory strands are equally depressed in conducting power. At first there is only induced a diminution in conductivity, and this accounts for the weak sensory impulses from the skin being impeded, while stronger stimuli pass. The motor impulses from the centres are also sufficiently strong to pass the cocainised tract of nerve, and hence motor power is well retained. Alms has proved this on rabbits and frogs in the following way.

In a rabbit both sciatic nerves were exposed and electrodes applied to them. On the left side the strength of current required to cause tetanus of the leg muscles was fixed, and on the right side the strength of current required to cause the rabbit (1) to raise its head sharply, and (2) to cry out. The left sciatic below the electrodes, and the right sciatic above the electrodes, were then painted with a 5 per cent. solution. By repeated stimulation the loss of conductivity could be followed, motor loss on left side, sensory loss on right side. The result was that in the right leg there was complete anæsthesia of the skin at a time when the rabbit showed signs of pain with a current applied to the right nerve-stem only a little stronger than was required before the painting with cocaine. On the left side motor conductivity diminished in an equal ratio. The end-result was complete loss of conductivity in the same time on both sides, proving that after direct application of cocaine to a mixed nerve, sensory and motor conduction become diminished in an exactly equal degree.

The same thing happens when the whole frog is brought under the influence of small doses of cocaine by subcutaneous injection, but it is in the spinal cord, and not at the periphery, that conduction is interfered with. The motor and sensory tracts in the cord (and probably the mixed nerves to a very much less degree) are at first slightly depressed. Gentle stroking of the skin has therefore no effect in causing a reflex, as it is not felt, its intensity being insufficient to pass along the partially paralysed nerve-tracts, or produce a sensation in the sensory centres. A severer stimulus (pinching skin, or direct stimulation of a nerve stem) is, however, readily conducted, and we get a violent reflex of the whole body. The motor conduction is slightly depressed, just as the sensory is, but as a pinch is sufficient to overcome the sensory depression, so the discharge of motor energy from the grey cells is sufficiently strong to overcome the slight motor depression. As the poisoning gets deeper after large doses, sensory and motor conductivity both gradually become quite abolished. The dulling in the perception of skin sensory impressions accounts for the flaccid attitude of the frog and the loss of good co-ordinating power which ensues almost immediately after the administration of cocaine. As Vulpian has shown, a frog keeps itself in its ordinary upright position by means of slight stimuli passing from the skin to the sensory and co-ordinating centres. When the skin of one leg is anæsthetised, this leg only lies flaccid, but when, by internal administration of cocaine, the sensory paths in the cord are depressed, the slight sensory impressions from the whole area of the skin are no longer conducted to the centres, and the animal thus loses the external stimuli by which it keeps itself upright and steady. Hence the limpness and flaccidity of its attitude. It feels a pinch, however, and kicks out violently at once, although lying flat on its belly and unable to jump, owing to loss of sensory impressions, and consequent loss of co-ordinating power.

With medium doses the power of perceiving severe stimuli and answering by a more or less marked movement is never abolished, although the movements are sometimes extremely feeble. As we have seen in the experiments above, the depression gradually passes off, and is succeeded by an increase in the reflexes. How and to what extent the implication of the encephalon affects the symptoms, is difficult to say. It is certain, however, that part of the general torpor is owing to brain depression.

Medium and Large Doses.—When 0.01 to 0.02 gramme is given to a frog, the effects are much the same as with smaller doses, but are more marked, while the motor nerves are, in addition, greatly affected. The torpor comes on more rapidly, is much more profound, lasts longer, and may pass into complete sensory and motor paralysis. The pupils are diminished in size to mere slits. The reflexes are at first quite abolished, then later on the torpor becomes less deep, and one gets a very flaccid tetanus on stimulation, the depression finally passing off, to be succeeded by great exaggeration of reflexes.

The motor nerves become diminished in their electric irritability early in the poisoning, but in addition to this their condition later on is peculiar, and comparable to that of the spinal cord, namely, a condition in which they become very rapidly and easily exhausted. If, some time after administering to a frog a large dose of cocaine, the sciatic nerve be exposed and stimulated with the interrupted current, it is found that whether the stimulation be rather weak, moderate, or strong, the muscles of the same leg contract, although not with their normal violence. On repeating the stimulation immediately after, an extremely feeble contraction may be obtained, or more usually none at all, and on the third stimulation no contraction occurs, although the muscles are quite excitable to direct application of the electrodes. If the nerve be then allowed a very short rest ($\frac{1}{2}$ to 1 minute or thereabouts) the application of a weak current to it again causes the muscles to contract. The motor nerves, therefore (like the cord with small doses), are in a condition not so much of complete paralysis, as of partial paralysis with great tendency to exhaustion, at least if their inability to conduct electric stimuli to the muscles signifies exhaustion. The voluntary muscles at the point of injection are generally less excitable than those which have not come into contact with the cocaine solution, but, except in one or two instances, the difference was trifling. Gramme 0.04 to 0.045 is a lethal dose.

Direct Application to Spinal Cord.—The direct application of 2 to 4 drops of a 1 per cent. solution cocaine hydrochlorate to the exposed spinal cord causes general symptoms similar to those seen after subcutaneous injection. In some cases there was a slight preliminary increase in the reflexes, but soon the frog lies on its belly, and shows the same indifference to stroking of its skin, while it responds to a severer stimulus with a tetanic but rather flaccid kick-out, each of these being followed by great exhaustion. The ability to localise the position of an acetic acid paper is also lost. The flaccid tetanic condition is sometimes, especially at first, very well marked, but if we apply too much of the solution, there is paralysis from the beginning. It is evident that all the more prominent symptoms induced by 2 to 3 milligrammes subcutaneously may be obtained when the cord alone is subjected to the influence of cocaine, and hence we may conclude that in such cases the symptoms depend chiefly on implication of the cord. When large doses are given subcutaneously, the depression of the peripheral nerves must contribute largely also to the paralysis.

Summary.—To summarise in very general terms the action of cocaine on the nervous system of the frog, we find (1) that it depresses the energising or conducting power of all forms of nerve-tissue; (2) that the grey cells of the cord are affected in a manner which causes them to discharge their energy violently, but also to exhaust themselves rapidly; and (3) that the spinal depression passes off, and is succeeded by a condition of greatly increased reflex excitability.

Experiment x.—Rana esculenta, 38 grammes. 12.2. 0.01 cocaine hydrochlorate in $\frac{1}{2}$ cubic centimètre under skin of back. 12.7. Gradually became more and more torpid and paretic, until it is now unable to jump. 12.10. Lying quite flaccid, but, if pinched, kicks out violently. 12.14. When pinched sometimes responds by a slight twitch, sometimes gives no response; pupils very contracted. 12.38. No response when pinched; sciatic nerve stimulated at 180 millimètres (Du Bois induction coil) = one faint twitch of muscles; stimulation at 0 = same. On second stimulation with either strength there is no contraction of muscles unless a short interval has elapsed; no reflex in other leg. 6.15. Frog still very flaccid, but has recovered somewhat; sciatic stimulated at 180 millimètres = a muscular contraction each time, while the stimulation causes at same time reflex twitch of other leg and of body.

Second day. Frog lying on belly with legs extended, and still very flaccid. On pinching, gives a limp tetanic extension of legs succeeded by great exhaustion; sciatic at 160 millimètres = every time marked contraction of muscles of same leg; the other leg contracts reflexly on the first stimulation of sciatic, but there is no reflex on the second stimulation; pupils are large. 3.0. Sitting up; reflexes much increased; pupils large.

Third and fourth day. Active and lively; well-marked increase in reflexes.

Fifth day. Is now about normal.

Experiment XI.—Rana temporaria; 37 grammes. 2.53. 0.02 cocaine in 8 minims of water+HCl *q.s.* under skin back. 2.54. Jumps very heavily. 2.55. Reflexes diminished; lying flat on belly, cannot jump, but kicks out forcibly with legs. 3.0. Quite flaccid and reactionless; pupils very small. 4.20. Sciatic nerve is very slightly excitable to strongest current, and on stimulating it no reflex movement of other leg is produced.

Second day. When pinched gives faint twitch; sciatic nerve on stimulation = faint contraction, on second stimulation = *nil.*

Third day. When pinched gives one marked twitch of abdominal muscles and slight twitch of rest of body, but on repeating the irritation no response is elicited unless an interval occur. Sciatic stimulated at 100 millimètres = feeble contraction of muscles, at 20 millimètres = well-marked contraction; but on second stimulation with either strength of current there is no response until a short rest has been allowed. Muscles all seem to contract well on direct application of electrodes.

Fourth day. Is respiring; pupils dilated, corneal reflex very active; when pinched gives a slight twitch. Sciatic stimulated at 120 millimètres = faint muscular contraction each time, while a stronger current causes more violent contraction. 6.0. Much recovered, sitting up; very great increase in reflexes.

Fifth and sixth days. Marked increase in reflexes.

Seventh day. About well; pupils still much dilated.

Action on Mammalia.—It is difficult to analyse the action of cocaine on mammalia with the same minuteness as in frogs, owing to the early occurrence of death from paralysis of the respiratory centre. Their higher cerebral development, with the consequent well-marked psychical symptoms, also complicates matters. Very excellent descriptions of its action on the higher animals have been given by von Anrep and U. Mosso, and to their papers I must refer the reader for details. The observations on man have been carried out chiefly with preparations made from the leaves, and therefore containing a mixture of the alkaloids.

On the Brain.—A comparison of the action of drugs on the brains of frogs and the higher mammals opens up a very wide question, but at present we may refer to three well-known substances which are commonly regarded as cerebral stimulants—alcohol, morphine, and caffeine.

After a dose of alcohol a frog at once shows symptoms of cerebral depression, but in the higher mammalia there is a stage of apparent stimulation. It is generally recognised, however, that the excitement is due to paralysis of the higher centres, and consequent loss of inhibitory and co-ordinating power between the different parts of the brain.

Morphine also from the beginning paralyses the brain in frogs, but regarding its action (especially in minute doses) on mammalia, there is considerable difference of opinion, some authors holding that it paralyses from the commencement, and that the apparent stimulation is really due to this,[41] while others consider it as having a primary directly stimulating effect on the grey matter of the cerebrum.[42] With very small doses it is said to have only this latter action, which, with larger amounts, is thought to be more or less completely masked by the subsequent narcosis.

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[41] Witkowski, *Archiv f. expt. Path.* vii, 247.

[42] Harley, Old Vegetable Neurotics; Nothnagel and Rossbach, *Arzneimittellehre.*

With caffeine there are in the frog no special brain symptoms, but in mammalia there is long-continued stimulation followed by exhaustion. No primary depressing effect on the brain has ever been described, but Filehne[43] has shown that in the frog there is depression of the cord before the advent of increased reflex excitability.

In large doses all these bodies act as paralysants, but there can be no doubt that in small amounts they increase the working power during mental or muscular exhaustion. Whether they do this by stimulating or paralysing certain parts of the nervous system has yet to be definitively determined. Experiments on man with coffee, alcohol, and morphine[44] have shown that small quantities shorten the reaction time, while Freud[45] states that cocaine also does so. These bodies, therefore, in not too large amounts, certainly increase the rapidity of nervous action.

The cocaine action seems to lie midway between that of morphine and caffeine. Caudwell[46] found on himself that small doses (half a grain hydrochlorate of cocaine) caused drowsiness, while larger doses caused only transient drowsiness, followed by persistent wakefulness and power of work.

Small amounts carefully administered to rabbits also cause well-marked quietude. With medium or rather large doses one often sees great excitement, and symptoms of inability of different parts of the brain to work in harmony and to control each other.

The subjective phenomena bear in some respects a close resemblance to those observed after not very large doses of morphine, while, on the whole, more nearly resembling those of caffeine. The exalted feeling of general well-being is, however, more marked than with the latter.

Von Anrep describes in dogs, after very large doses, constant restlessness and hallucinations, the whole train of symptoms reminding one of a case of acute delirious mania in man. Magnan and Saury[47] also describe hallucinations of sight, hearing, and smell in three cases of cocaine habit, but less marked than one sees in delirium tremens. There were present in addition difficult ideation and delirium. It is possible that such symptoms may arise from overstimulation of the brain, but the most probable explanation is that they are due to paralysis. The experiments of Tumass (direct application to the cerebral cortex), and the general symptoms after large doses, bear out this view. It seems probable, however, that the secondary effect of small doses is that of a direct cerebral stimulant.

Different individuals react very differently to all such substances and to different dosage, a fact which has been specially drawn attention to by Mosso in the case of dogs with cocaine.

The actions and symptoms are otherwise essentially the same as in frogs. A dog, after hypodermic injection of cocaine, may become less lively or excited according to temperament, but there is always loss of co-ordination and indifference to stimuli. General sensibility becomes much depressed, and the symptoms of alterations in sensibility precede the symptoms of motor paresis. Mosso says that when a dog was still standing up and able to move about, he could press with the whole weight of his foot on its hind toe without causing a movement. The convulsions, when present, come on at intervals, and are succeeded by great exhaustion. They are said not to be reflex, but to depend on stimulation of the medullary centres. Both Mosso and von Anrep, however, found that the spinal cord is in a state of increased excitability, but is less sensitive to stimuli from the skin and can be readily exhausted, just as we have seen to be the case in frogs.

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[43] Filehne, *Archiv f. Anat. u. Physiol.*, 1886, 72.

[44] Dietl and Vintschgau, *Pflüger's Archiv* xvi, 1878, 316.

[45] Freud, *Cbl. f. d. med. Wiss.*, 1885, 636.

[46] JOURNAL, 1885, i, 17.

[47] Magnan and Saury. *Comptes Rend. de la Soc. de Biol.*, 1889, 60.

I have found in rabbits that the convulsions may be prevented by keeping up artificial respiration. A similar observation has been previously made as regards caffeine and strychnine, but the exact reason is unknown. In mammalia, death occurs always before the motor nerves are appreciably affected. Mosso states that with very large doses in dogs death may occur with symptoms of paralysis only.

Cocaine has a very marked action as a general analgesic, besides its local anæsthetic action. Livierato[48] found that its subcutaneous injection at any point eases the pain in neuralgia, and hence its effects must be central as well as local. The following experiment by Grasset,[49] shows the same thing even more clearly. He injected 0.01 gramme of cocaine hydrochlorate under the skin of the abdomen in a monkey, producing local anæsthesia in five minutes. After seven minutes, however, pinching the nose, touching the cornea or irritating the larynx called forth no reflex. The animal was perfectly quiet and sensible. This condition lasted for eighteen minutes. It is difficult to say how much the brain was affected in such a case, but the conducting power of the cord must have been greatly diminished. Magnan and Saury report a certain degree of analgesia in their cases, while Laborde[50] also regards it as diminishing general sensibility (guinea pigs), but from cerebral causes. On the other hand, Arloing[51] and Laffont[52] hold that it has this action only in very large doses.

Hepburn[53] has found, on himself, that after repeated injection of small doses there was general diminution of tactile sensibility, so that he felt as if he were standing on cushions, an observation which I can confirm from my own experience. It is hardly necessary to point out again that this is a symptom seen in locomotor ataxy, and that it is due to deficient conduction of sensory impressions by the cord. The latter is certainly the most potent factor in the diminution of general sensibility, much more so than any narcotic action on the brain. As the implication of the spinal cord has been already so fully discussed in the case of frogs, it is unnecessary to go into the matter further.

Experiments with Cocamine.—The alkaloid was given dissolved in a very dilute hydrochloric acid solution, exactly neutral in reaction, and freshly prepared each day, as it is very apt to decompose. When administered in small doses cocamine has a very evident and marked action as a general stimulant. The frog shows this well, becoming alert, excited, restless, and capable of taking leaps much in excess of its usual performance. There is a faint increase in the reflexes; the muscles respond with great sharpness to the nervous impulses, and thus there is brought about the change in the animal's bearing. Such effects are seen with $\frac{1}{2}$ to 1 milligramme subcutaneously, and last for the greater part of a day. When this dose is increased to 2 milligrammes, the symptoms observed vary a good deal in different cases. They may be similar to those just described, but more usually, along with a slight tendency to increased reflex, we get signs of nervous and muscular depression, such as loss of precision in movement, resting head on table, indifference to stimuli, slowing of respiration, unwillingness to move, and muscular stiffness. Although the spinal reflexes are increased, the cord tends to rapid exhaustion of the nature described under cocaine. The pupil is dilated. The symptoms of depression of the nervous system usually pass off in a few hours, but the increased reflex and the muscular stiffness persist for many days. There is always deep anæsthesia at the place of injection, and the motor nerves may be also slightly depressed in excitability.

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[48] Livierato, *Lavori dell' Istituto di Clinica Medica di Genova* ii, No. 4 (quoted by Alms).

[49] Grasset, *Comptes Rend.*, xcix, 983, 1884.

[50] Laborde, *Comp. Rend. Soc. Biol.* (8) i, 631, 645, 747, 1884.

[51] Arloing, *Mém. Soc. Biol.* (8) ii, 15, 1885.

[52] Laffont, *Comp. Rend. Soc. Biol.* (8) iv, 741, 768, 1887.

[53] Hepburn, *New York Med. Record*, 1884, ii, 534.

With 4 to 5 milligrammes there is sometimes no, sometimes a very short, period of stimulation followed by deep depression, but by next day the latter has usually passed off, leaving only the spinal and muscle symptoms. Such doses may or may not prove fatal. With large doses (0.01 gramme) there is generally no preliminary stimulation, but there sets in a rapidly-deepening paralysis of the nervous and muscular systems. In a short time (usually about a quarter of an hour) the frog is quite flaccid, respiration ceases, the pupils are extremely small, and the animal responds to severe stimulation only by a slight twitch. The condition of the cord and motor nerves is practically the same as in cocaine poisoning, but there is much greater paralysis and tendency to exhaustion of the cord, while the flaccid tetanic explosions are not nearly so violent nor so readily called forth. The motor nerves are also more profoundly affected than after cocaine, for if, when the frog is in this condition, the sciatic nerve be stimulated with any strength of current, only a mere twitch of the leg muscles ensues on the first application of the electrodes, and none on the second. One centigramme is always a lethal dose if given subcutaneously. After its administration the muscles at the point of injection soon become less excitable, and are generally dead in about an hour, while the more distant muscles only very slowly become impaired in irritability. When the alkaloid is given by the mouth the muscles are poisoned more gradually and equally, those which receive the largest blood supply dying soonest, but usually only after some days.

Cocamine is an extremely active muscle poison, and on injection subcutaneously is rapidly absorbed by the neighbouring muscles, which pass into a condition of rigor mortis, if the dose be large enough. From what has been previously said, however, it is evident that with small amounts the muscle protoplasm must suffer only such changes as can be recovered from with comparative ease, and which do not proceed so far as rigor mortis. With large doses the local rigor gradually spreads to the more distant muscles, those which receive most blood being most affected. Frequently after death the muscles furthest from the heart, such as those of the forearm and leg, contract quite well to electric stimulation, while all the others are non-excitable. If the solution be injected into a fleshy part, such as the thigh, we may often enough find that one half of a muscle is quite dead and non-contractile, while the other half, which has not absorbed the cocamine solution, contracts apparently as usual. Gradually, however, the whole muscle dies. Stronger proof could hardly be given of the great tendency of muscle protoplasm to absorb these bodies.

The contraction of the muscles as they pass into rigor mortis may alter the attitude of the frog, the spinal column being bent round one way or the other, according as the injection has been made under the skin of the chest or back. Non-striped muscle is also acted upon, but the effects can be better observed in mammalia. The heart is considerably affected, becoming slow and feeble, and usually stopping in diastole much dilated with blood. When the ventricle has ceased to beat, the auricles often keep on for some time longer. In one or two cases the heart was found empty, contracted, and with a shrivelled appearance.

With large doses death in frogs is due to stoppage of the heart, usually on the first day, while with smaller doses it frequently occurs many days after administration from exhaustion and muscle poisoning.

In experimenting with 2-milligramme doses, I noticed very great differences in the effects on different frogs, these being probably explainable by the amount of the poison absorbed by the muscles locally. If the cocamine be all so absorbed at once, then the nervous system is only affected when the alkaloid leaves the muscles and gets into the blood; it enters the circulation slowly, and produces slight but long-continued increase of the spinal reflexes. If, however, part of it enter the circulation at once, we immediately have symptoms of spinal excitement or depression, according as the amount is small or great. If the cord itself be exposed, and a solution of cocamine directly applied to it, we find that we get increased reflex or extreme paralysis according to dosage. When given *per os*, its excessive action on the local voluntary muscles is avoided, but the symptoms are, generally speaking, the same as by subcutaneous injection. The only difference in its action on the two species of frog seemed to be that rana esculenta requires rather larger doses than rana temporaria to produce the same effects, while in the former the muscles are not so susceptible to the action of the alkaloid.

Comparing its action on frogs with that of cocaine, we see that in very small doses cocamine has a great tendency to cause increased reflex excitability. Larger doses act on the nervous system as cocaine does, but more powerfully, and a much smaller amount is lethal. Lastly, its action on muscle is much more marked, and complicates the symptoms somewhat.

Experiment XII.—Rana temporaria. 33 grammes. 11.26. 0.002 gramme cocamine in $\frac{2}{3}$ cubic centimètres subcutaneously. 11.35. Has been very active and lively, and takes very long jumps. 12.0. Has been constantly active; pupils very dilated. 12.20. Slight increase in reflexes; very active. 3.40. Still same; jumps great distance, 4.30. Same faint increase in reflexes and great activity.

Second day. All effects passed off except faint increase in reflexes.

Experiment XIII.—Rana temporaria. 32 grammes. 11.26. 0.002 gramme in $\frac{1}{3}$ cubic centimètres under skin of chest. 11.35. Very active, but jumps with slight loss of precision. 11.45. Not so lively, but jumps well and actively. 12.0. Head resting on table; very unwilling to move; there is now increase in reflexes; pupils large. 1.10. Increase of reflexes much greater, otherwise same. 2.40. Sitting up; active, pupil dilated, reflexes greatly increased. 4.20. Same.

Second day. Active and lively; reflexes increased; unwilling to jump owing to shock on landing.

Third to fifth day. Slight increase in reflexes.

Sixth day. Reflex increase passed off: great muscular weakness.

Seventh to thirteenth day. Gradually became unable to move.

Fourteenth day. Died; muscles of chest and of back quite irresponsive to electric stimulation; those of legs and arms impaired.

Experiment XIV.—Rana esculenta. 48 grammes. 12.4. 0.01 gramme cocamine in ¼ cubic centimètre under skin of chest. 12.7. Has been jumping about actively. 12.9. Much less active; respiration slowed; pupils medium. 12.11. Can scarcely jump; reflexes diminished. 12.15. Head on table; respiration ceased; lies on back; pupils smaller; gives only a faint twitch on severe irritation; sciatic nerve exposed and stimulated; on first stimulation there is a slight twitch of leg, and on second stimulation no movement; the stimulation calls forth no reflex in other leg. 5.15. Has remained same; muscles at point of injection contract very feebly with strong current; other muscles about normal.

Second day. Heart stopped; muscles at point of injection do not contract, others are slightly impaired.

Experiment XV.—Rana temporaria. 24 grammes. 1.28. 0.01 cocamine in solution *per os.* 1.50. Has gradually become a little more sluggish. 2.0. More disinclined to jump; chin on table, but if irritated jumps very well; lies on back if quietly placed there; faint increase in reflexes. 2.15. Very distinct increase in reflexes; pupils large. 2.30. Reflexes much increased; gives a violent start if touched. 3.15. Very great increase in reflexes, but not tetanus. 3.40. Slightest stimulation now brings on a tetanic spasm, but of short duration, and succeeded by great exhaustion. 4.30. Same.

Second day. Still considerable increase in reflexes. There was a gradual return to normal.

Experiment XVI.—Rana temporaria. 27 grammes. 12.45. 0.025 cocamine in solution *per os.* 1.0. Lies flaccid, chin and belly on table; if irritated, kicks out legs, but cannot jump. 1.15. is now very flaccid; if leg be pinched there is only a feeble twitch or no response; cannot jump, ceased to respire; corneal reflex present; pupils large. 2.15. Strong interrupted current applied to motor nerves causes very slight muscular contraction. 2.45. Gives no response on irritation; lying as if dead.

Second day. Sitting up; jumps well; reflexes greatly increased.

Third day. Reflexes much increased.

Fourth day. Very slight increase in reflexes; lying very limp and depressed, and shows signs of great muscular weakness; can no longer jump. 12.30. Died; heart in diastole; all the muscles impaired, but none dead; nerves are quite excitable.

Mammalia.—When 0.03 to 0.04 gramme is given subcutaneously to a rabbit, there may be no symptoms, but sometimes restlessness and mental excitement are seen. Gramme 0.05 causes in a few minutes great dilatation of pupils, restlessness, and slight but well-marked increase in the reflexes. All this passes off in an hour or so, and is succeeded by a distinct desire to sit quiet and not move about.

Gramme 0.08 gave more pronounced symptoms—marked restlessness, great dilatation of pupils, tremulousness, and slightly increased reflexes. But the most typical effects are weakness of gait, depression of general sensibility, and tendency to lie down, while the mental faculties seem quite active. When roused, the rabbit runs about actively, but as soon as it is left to itself subsides again. Respiration is somewhat quickened; the heart maintains its rate, but the beat is usually feebler.

Gramme 0.1 always proved a fatal dose (1290 to 2080 gramme rabbits), death sometimes occurring in a few minutes from paralysis of respiration, sometimes only after several hours. In the latter case there was always enormous dilatation of pupils, indifference to stimuli, and great muscular weakness, the animal lying down and sprawling out its legs. Sometimes there was no increase in the reflexes, but usually the rabbit gave frequently slight spontaneous starts, which could also be elicited by stimulation. The heart became feeble and fluttering, but usually maintained its rate, while the respiration became quickened, superficial, and panting in character.

Two grammes given by the mouth caused great depression lasting for about five hours, while 5 grammes proved fatal after twelve hours. In both cases there were no signs of increased spinal excitement, but simply great muscular depression.

In cats (1680 to 2400 grammes) 0.3 to 0.4 gramme was a lethal dose administered subcutaneously. Small doses caused excitement, dilatation of pupils, twitching of tail, ears, and muscles of head and neck, while 2 decigrammes or more produced great muscular and nervous depression, frequent vomiting, severe diarrhœa, and great weakness of gait. There was either no, or a very slight, increase in the reflexes. When given by the mouth it was invariably rejected sooner or later, so that no symptoms beyond depression and severe vomiting were observed. In cats death occurred always many hours after administration.

The detailed symptoms of the action of cocamine on rabbits and cats will be found in the experiments given below. The *post-mortem* appearances are worthy of particular attention, as they throw great light on its mode of action and the cause of death. In rabbits and cats they are practically identical. On opening the abdomen immediately after death, peristalsis of the stomach and bowel is seen to be going on with remarkable energy. Particular bands of muscular fibres contracting powerfully at intervals frequently give the stomach an hour-glass appearance, while less violent contractions pass continuously over the whole surface of the viscus. The bowel is in a similar condition, with a thick, firmly-contracted wall and much diminished lumen. The bladder is empty and strongly contracted.

At the point of subcutaneous injection the muscular fibres no longer respond to electric stimulation, while the other muscles contract quite well or feebly, according to the time which has elapsed between administration and death. If death have occurred rapidly, they have not had time to get thoroughly poisoned. The sciatic nerve is sometimes quite normal in excitability, or may be more or less dulled. Rigor mortis comes on very quickly, and is very marked. The heart is sometimes in systole, sometimes in moderate diastole.

We see, therefore, that in mammalia cocamine is a muscle poison, and exercises on the nervous system an action resembling that of cocaine. The cause of death, when it occurs slowly, is due to gradual poisoning of the respiratory muscles; while when it occurs rapidly it is from paralysis of the respiratory centre. The motor nerves are never sufficiently affected to be paralysed. The vomiting and diarrhœa are due to the violent contraction of the walls of the alimentary canal. In mammalia, when given by the ordinary channels, there are no marked symptoms of stimulation of the central nervous system. All we can observe is slight mental excitement and a slight increase in the spinal reflexes, but these are greatly thrown into the background by the muscular depression and the indifference to severe stimuli. Cocamine is probably so rapidly absorbed by the muscles that only a small quantity ever reaches the spinal cord. To ascertain whether direct injection into the blood would cause its carriage to the central nervous system, I administered 0.05 gramme in 1 cubic centimètre to a rabbit *per venam jugularem*, but death ensued at once, apparently from paralysis of the heart. The animal gave a few gasps and expired. In another rabbit, 0.03 gramme was injected into the left femoral artery. The animal was at first rather collapsed, and could not sit up, but recovered greatly in about half an hour. There were no symptoms of increased reflex. Four minutes after the injection it was observed that the left leg was quite helpless. Three hours after administration the rabbit was killed, it being then apparently quite normal, with the exception of paralysis of the left leg. All the muscles supplied by the femoral artery below the point of injection were quite dead, all other muscles of the body being apparently normal. In the left thigh the lower parts of many muscles were non-excitable to the strongest currents, while the upper parts reacted quite well. The left sciatic nerve was also non-excitable, motor nerves elsewhere being normal. It is evident, therefore, that the muscles locally must absorb the isatropylcocaine to a large extent, and prevent it reaching other parts of the body in sufficient quantity to give rise to very marked symptoms.

Direct injection of a solution into the cord was also tried. The spinal cord of a rabbit was exposed under ether, and, when the animal had recovered from the anæsthetic, 0.005 gramme in solution was injected posteriorly into the cord substance. In about one minute there was complete motor and sensory paralysis of the posterior half of the body, while the anterior half did not seem at all affected. After waiting some hours the animal was *in statu quo*, and then the same quantity was injected anteriorly. Paralysis rapidly ensued from behind forwards, and the animal died in a few minutes from failure of respiration. I did not care to repeat this experiment with much smaller doses, as the results on frogs showed conclusively (as well as the general symptoms) that, if the dosage be chosen sufficiently small, we get a marked increase in the reflexes.

Experiment XVII.—Rabbit. 1,290 grammes. Heart 30; respirations 19 in ten seconds. 12.5. 0.1 cocamine in 2 cubic centimètres subcutaneously. 12.7. Pupils widely dilated; respirations 17. 12.10. Active, lively, and running about; pupils very dilated; heart 30; respirations, 25. 12.12. There is very great trembling of legs and body, and reflexes seem slightly increased; legs are sprawled out at right angles to body. 12.16. Heart 29; respirations, 26; pupils enormously dilated; occasionally gives a slight spontaneous start, and reflexes slightly increased on stimulation; chin rests on table. 12.18. There is extremely marked, and rapidly increasing muscular weakness. Animal lies now on belly, half resting on one side with chin on floor; cannot stand up; gives on stimulation a slight start; respiration 15. 12.22. Much worse; lying quite flaccid and collapsed; pupil, small medium; respiration 7, deep and laboured; does not start on stimulation; heart cannot be felt. 12.25. Died quietly.

Experiment XVIII.—Cat. 2,600 grammes. 11.36. 0.2 cocamine in 5 cubic centimètres subcutaneously. 11.40. Pupils larger, salivating. 11.41. Vomited. 11.44. Pupils very dilated; looks about suspiciously, and twitches tail; no increase in reflexes. 11.48. Vomited and defæcated; gait feeble. 12.0. Gait feebler; lying down; head, ears, and jaws twitch frequently; pupils very dilated. 12.2 Vomited. 12.12. Very extreme weakness in gait, can scarcely stand, and is very limp: gives an occasional twitch of tail or one leg. 2.0. Has been salivating a good deal; is very weak. 3.30. Weakness has increased; lies on belly, and when raised up its legs sprawl out, and are unable to support it; pupils dilated; there has been no trace of increased reflex on stimulation. 3.45. Vomited after violent retching. 5.0. Very depressed, but recovering slowly.

Second day. During night has had violent diarrhœa.

Third day. Is still weak, but rapidly recovering.

Anæsthesia.—When locally applied in neutral solution cocamine salts exert an anæsthetic action, which is not, however, anything like so powerful as that of cocaine salts. The base itself may be kept in the mouth for a long time, and no trace of numbness be felt. It is both weak in action and very insoluble in water, and hence the absence of numbness.

The following experiments show, more clearly than any description, the extent and duration of local anæsthesia, after the application of cocamine.

Experiment XIX.—Rabbit. 10 per cent. solution in hydrochloric acid and water. 3.52. Four drops in left eye; shut eye at once, and evidently felt some smarting. 3.56. Sensitiveness of left cornea much diminished, but not abolished; not much irritation. 4.5. Feels touching cornea with needle, but not acutely. 4.20. Anæsthesia is still very considerable, but is beginning to pass off; cornea hyperæmic. 5.0. Anæsthesia now very slight. There is a good deal of irritation of cornea and conjunctiva. 5.20. Anæsthesia completely gone.

Experiment XX.—Rabbit. 5 per cent. solution. 2.15. Four large drops in left eye; winked frequently and rubbed eye with paw. 2.19. Slight anæsthesia; cornea hyperæmic. 2.21. Anæsthesia marked, but not complete. 2.26. Anæsthesia gradually passing off. 2.28. Is quickly passing off. 2.30. Both corneæ equally sensitive; left is irritated.

Experiment XXI.—Experiments on my own eye; 10 per cent., 5 per cent., and 2½ per cent. solutions were used. There was always some irritation, even when the solution was quite fresh. When the solution was prepared for more than a few minutes it became brownish and caused great pain, in some cases as marked as if pepper had been thrown into the eye. There was always immediate hyperæmia, and sometimes a persistent feeling of dryness and swelling.

Two and a half per cent solution fresh. 3.38. Three drops in left eye; there was at once slight smarting and hyperæmia. 3.42. Left cornea less sensitive than right. 3.45. Distinct but not great impairment of sensitiveness. 3.55. Both corneæ equally sensitive; left is a little hyperæmic and feels dry.

No dilatation of the pupil was ever observed. A 10 per cent. solution applied to tongue for 10 to 15 minutes only caused very trifling numbness.

Regarding the light which the foregoing investigation throws on the relation between the chemical constitution and physiological action of the coca alkaloids little can be said. Cocaine itself affects chiefly the nervous system, first as a transient depressant, and then as a stimulant, the action on muscle being feeble. When by losing methyl, which is replaced by hydrogen, benzoylecgonine is formed from it, we have from the first a stimulant action on the nervous system and on muscle, both of which actions may become paralysant with a large dose. When benzoyl is eliminated to form ecgonine, the same actions remain, but much milder. It is evident, therefore, that such changes as the substitution of methyl or benzoyl for hydrogen exercise a marked influence on the action of the molecule, but no general conclusions can be drawn regarding other alkaloids. It is probable, however, that in different alkaloids the effect of such substitutions on the action will vary considerably. The cocamine action resembles that of cocaine in many ways, but it exercises a profound influence on muscle, while that of cocaine, although visible, is slight. If its constitution is the same as that of cocaine, then we must conclude that the substitution of the isatropic acid for the benzoic acid radical is the cause of the difference. Both are diethers of ecgonine, but in the one case the muscle-action of ecgonine is lessened, while in the other it is greatly increased. Definite knowledge on these points can only be obtained by a systematic investigation of all the homologues of cocaine.

Hygrine.—This body was first named and described by Wöhler[54] as a volatile liquid alkaloid obtainable from coca leaves, and forming a crystalline but very hygroscopic hydrochlorate. A few drops given to a rabbit had no effect on it. Lossen[55] describes a method of isolating it, and characterises it as a brown oily liquid of high boiling point, strong alkaline reaction, and burning taste, with the usual properties of volatile alkaloids. By distilling amorphous coca alkaloids in a current of steam I obtained a body[56] which was recognised as being identical with Wöhler's and Lossen's hygrine.

Dr. Hesse[57] has also described it, and as the following experiments were made with a specimen which he kindly prepared for me, I shall give his method at length. The mother liquors from, or the amorphous coca bases themselves, were distilled in a current of steam, when the hygrine comes over mixed with water. The distillate was treated with slight excess of hydrochloric acid, evaporated, and then treated with excess of caustic soda. The mixture was then shaken up with ether, which dissolves the hygrine, the ethereal solution was drawn off, and the ether evaporated, leaving the hygrine. The latter was further purified by repeating the process of solution and precipitation. It is a dark brown oily liquid, with a peculiar smell and burning taste, and has all the properties of a volatile alkaloid. The hydrochlorate is non-crystalline, yellowish white, and has the peculiar smell and taste of the base itself.

Its existence has been denied, and its composition and exact source are unknown. It is possibly a pyridine base formed by the decomposition of another alkaloid, or it may be one of the ecgonine compounds got on decomposing cocamine.[58] Whatever it is, however, it derives a practical interest from its extremely irritating action.

When one drop is injected under the skin of a frog, there ensues almost at once intense local hyperæmia, and after a few minutes there is intense depression and collapse. In a short time the animal lies as if dead. On reflecting the skin at the place of injection, there is found serous and bloody exudation, while the muscles are infiltrated and friable. This and the collapse seem to be due to the intense local irritation. The heart is extremely feeble, but the motor nerves and muscles all over the body (except locally) seem normal. If the hygrine be distilled with water so as to dilute it, and then 10 to 20 minims of the distillate be injected, there is only slight depression and local hyperæmia. The animal remains rather dull for a day or two, and if it be then killed, slight hæmorrhages are found in the muscles and serous membranes throughout the body, due to intense local irritation from small particles of the base carried by the blood stream. The hydrochlorate, in doses of 0.001 to 0.01 gramme, had very much the same effect—intense local irritation, with more or less consequent depression.

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[54] Wöhler, *Liebig's Annalen*, cxxi, 372.

[55] Lossen, *Liebig's Annalen*, cxxxiii, 352, 1865.

[56] *Pharm. Journ. and Trans.*, (3) xvii, 861, 1887. *Ibid.*, xviii, 701.

[57] Hesse, *Pharm. Journ. and Trans.*, (3) xviii, 437, 1887.

[58] Hesse, *Berichte*,xxii, 665.

In rabbits, 0.02 to 0.1 hydrochlorate of hygrine given subcutaneously in solution caused no symptoms except local irritation. In small rabbits, 0.15 to 0.2 gramme caused depression, slight weakness in gait, and slight tendency to starting and tremors. There was intense irritation, with bloody exudation at the place of injection. The application of hygrine to my own tongue caused at once burning and tingling, the former soon passing off but the latter lasting for about an hour.

These experiments are unfortunately too few in number to draw any conclusions from regarding the action of hygrine, but in such doses as the above it seems to have little beyond the effects consequent on intense local irritation.

Having now examined to some extent the actions of the more important at least of the active principles of coca, we may, in conclusion, consider some of the more interesting questions with regard to the use of the leaves themselves. They have been used by the Peruvian Indians from time immemorial, and all travellers are unanimous in bearing testimony to their value in preventing or deadening the sense of fatigue and hunger, in supporting severe and continuous exertion on a spare diet, and in enabling persons to ascend hills and breathe the rarefied air of the Andes without distress. Most European observers have come to similar conclusions, those who have not done so having probably used spoiled leaves. Von Bibra says of coca: "It satisfies the hungry, lends new strength to the weary and fatigued, and makes the unhappy forget his griefs."

The Indians take it in repeated small doses, and it is thus that the greatest benefit is derived from its use, as a large quantity taken at one time produces toxic phenomena such as loss of co-ordination, paresis, incoherence of ideas, and various disagreeable sensations (Schroff, Ott, Mantegazza, and others). In this it resembles opium, alcohol, caffeine, and all similar substances. Further, in man, the beneficial effects of such drugs are most appreciated when the body or mind is exhausted, and, with doses which produce only subjective sensations of stimulation, showing no decided outward and visible signs of their action. Such doses cause no symptoms whatever in animals, and hence a study of their effects can only be made on man.

There is unanimity of opinion that the moderate use of coca is of direct benefit to the Indian in many ways, while excessive indulgence is extremely rare. In Peru and Bolivia no disgrace whatever attaches to its habitual use, but on the upper Amazons it seems to be held in reprobation (Bates). Regarding its action, the stimulating effects have been much more dwelt upon and brought into prominence than its tranquillising narcotic action. We hear chiefly of the feeling of buoyancy and lightness, the increased power of work and prolonged sleeplessness; but, with small doses especially, the initial effect is sedative. This narcotic action has been observed by several Europeans on themselves, but is well seen in the Indian, who, when he wishes to enjoy the leaf thoroughly, ceases work, lies stretched out at his ease, and masticates in complete silence and abstraction. Only then is the pleasure unalloyed, and nothing will induce him to interrupt the operation of chewing. Sometimes, when undergoing exceptional fatigue, the Indian chews coca almost continuously without knocking off work, but in such cases he can experience only its anæsthetic and stimulant effects, the surroundings being unfavourable to mental tranquillisation. The narcosis consists simply in a slight dulling of the central nervous system to sensory stimuli of all kinds, whereby a gentle dreaminess and abstraction from the outer world are induced, and this is followed by a much longer period of nervous and muscular stimulation.

There are thus obtained from coca the pleasurable effects both of morphine and caffeine, the chewer experiencing in the first place the soothing influence of the former, but avoiding its disagreeable after-consequences, their place being taken by a buoyant feeling more marked than that induced by caffeine. The complete absence of after-depression and mental confusion, results so often seen with opium, is attributable to this rapidly succeeding stimulant effect, and also, probably, to the fact that the coca alkaloids lessen external influences largely by depressing the conducting power of the spinal cord, and only to a comparatively slight extent the centres in the brain. Opium, on the other hand, exerts a prolonged dulling effect chiefly on the cerebrum, which is followed, not by stimulation, but by mental confusion and heaviness. Large doses of coca, however, do cause headache and mental unfitness next day (Ott), while frequent debauches completely break down the nervous system (Pöppig). The Indians lead very laborious and monotonous lives in a trying climate with insufficient food and clothing, and the *tædium vitæ* incidental to such an existence must be greatly relieved by the indulgence of coca chewing. It has a further benefit according to von Tschudi. The roasted maize, which constitutes almost their sole diet, tends to occasion severe obstruction of the bowels, but this is counteracted by the use of coca, an explanation of which is readily got from the marked action of the active principles in stimulating peristalsis. Nevertheless its excessive and prolonged use brings on obstinate constipation (Pöppig), probably from neuro-muscular paralysis of the bowel.

Its action in dulling the sense of hunger is readily understood from the local and central anæsthetic effect of cocaine and cocamine, while their subsequent stimulating properties enable the nervous system to functionate more actively, and thus overcome the sense of fatigue. The muscles also (as with caffeine) probably pass more easily into a state of contraction. Whether coca or caffeine have any effect in diminishing metabolism opens up a very wide, and as yet unsettled, question. The observations which have been made either with cocaine or with coca have not been carried out in a manner calculated to throw much light on the subject, while the results are contradictory. Moreno and von Anrep found that cocaine did not delay the death of rabbits by starvation. Ott, experimenting on himself, got a slight diminution in the amount of urea and urine excreted, while the pulse and temperature both rose. Carter[59] also saw a diminution in the urea, but Gazeau[60] got an increase, and Espinosa[61] states that both the urea and carbonic acid were augmented. Christison[62] thought it lessened the hourly excretion of urinary solids, but says expressly that his experiments were insufficient to draw conclusions from. Fleischer[63] found the urea and phosphoric acid diminished, but Da Costa and Penrose[64] got exactly opposite results with cocaine, while Bignon[65] is of opinion that metabolism is increased. Mason[66] has also made some observations, but I have not been able to obtain the original paper.

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[59] Carter, JOURNAL, 1874, i, 414.

[60] Gazeau, *Nouvelles Recherches expér. sur la Pharmacologie, etc., du Coca,* Thèse de Paris, 1870.

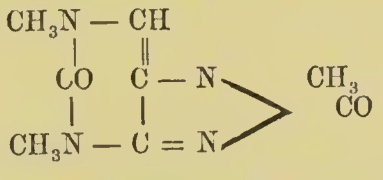
[61] Espinosa, Abstract in *Edinburgh Medical Journal*, xxi, ii, 1151, 1876.

[62] Christison, JOURNAL, 1876, i, 527.

But an investigation of the excretion of urea does not seem to me to be the proper method of determining the action of such substances on metabolism. The excretion of urea is very slightly affected by increased muscular exercise. The source of muscular energy is the carbohydrates of our food modified by the digestive processes, and the waste products of muscle activity are non-nitrogenous bodies. Hence, with an increase or decrease of chemical action in muscle, one would not expect the urea to be influenced. As we have seen, cocaine has little action on muscle, but cocamine and benzoylecgonine affect it profoundly in the same way apparently as caffeine does. The influence of caffeine on urea excretion has been frequently investigated with somewhat contradictory results, but this much is certain, that it makes very little difference one way or the other, so far as the total nitrogen excreted is concerned.[67]

It is conceivable, although no experimental data exist to support such a supposition, that such substances as cocamine or caffeine, which undoubtedly modify the vital processes in muscle even to the production of rigor mortis, may also affect its chemical activity, so that it is capable of performing an equal or greater amount of work with a lesser consumption of carbohydrates. If this were the case, these bodies would act as economisers of food (*aliments d' épargne, Sparmittel*) not in the generally accepted sense of preventing the breaking down of the nitrogenous body tissues, and thereby diminishing the excretion of urea, but in diminishing the consumption of non-nitrogenous substances by the muscles. It seems hardly probable that the wonderful power of endurance shown by the Indians, and their long fasts while undergoing excessive fatigue, can depend solely on stimulation of the nervous system. There must be at the same time an economising in the bodily expenditure, an idea which is further confirmed by the total absence of emaciation or other injurious consequences.

In passing, it may be interesting to point out that caffeine has an entirely different constitution from the coca alkaloids. It is not a pyridine base, but is trimethylxanthine (xanthin in which three hydrogen atoms are replaced by methyl) thus :



$C_8H_{10}N_4O_2$

If it be the case that coca diminishes the consumption of carbohydrates by the muscles during exercise, then less oxygen will be required, and we have ready to our hand an explanation of its action in relieving breathlessness while ascending mountains. At the same time we must not lose sight of the fact that such an effect has not been demonstrated, and that the stimulation of the nervous system is probably also an important factor.

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[63] Fleischer, *Deutsch. Archiv. f. klin. Med.*, lxii, 82.

[64] Da Costa and Penrose, *Philad. Med. News*, 1886.

[65] Bignon, *Bull. de Thérap.*, 1886.

[66] Mason, *Boston Med. and Surg. Journ.*, 1882.

[67] Voit, *Ueber den Einfluss des Kochsalzes, des Caffees, etc.* München, 1860.

As I have had considerable difficulty in collecting from original sources information regarding coca, it may lighten the labours of others if I add a bibliography. A number of physiological papers besides those quoted in the text have been published, and these I also give, but I have omitted all purely therapeutical and toxicological articles, as they are exceedingly numerous, and are to be found scattered through all the principal medical journals since 1884. The list, however, is by no means a complete one, as there are many Peruvian, American, and other foreign publications which I have been unable to obtain. Some of these are to be found in the Index Catalogue of Library, Surgeon-General's Office, United States Army, and in the various Dispensatories.

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